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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/891,873	06/26/2001	Jacobus Van Meel	0652.2300001/EKS/PSC/TAC	9032

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EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	9

DATE MAILED: 07/16/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/891,873	VAN MEEL, JACOBUS	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

1. This action is in response to Paper No. 8, filed April 24, 2002. Applicants arguments presented in the response of Paper No. 8 have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections and objections not reiterated herein are hereby withdrawn. This action is made final.

2. Claims 1-4, 6-13 and 17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods which monitor and evaluate the efficacy of an inhibitor of epidermal growth factor or epidermal growth factor receptor or the efficacy of NGF or TGF-β1, does not reasonably provide enablement for methods which monitor and evaluate the efficacy of any growth factor cancer drug by detecting a change in the level of telomerase activity in cells treated with said drug. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn broadly to methods for monitoring and evaluating the efficacy of a growth factor cancer drug wherein the methods comprise preparing a sample of cancer cells from a patient diagnosed with cancer and receiving therapy with said drug, determining the level of telomerase activity in said sample, comparing the level of telomerase activity in the sample with that of a control sample and correlating the level of telomerase activity with the therapeutic effect of the drug. The specification broadly discusses "growth factor cancer drugs" and this phrase has been interpreted to include any compound which alters the growth of a cancer cell, or which effects, directly or indirectly, any "component" of a signaling pathway of a member of a growth

factor family. The specification (pages 11-12) teaches that treatment of nu/nu mice xenografted with A431 or KB tumor cells with compounds which inhibit the epidermal growth factor tyrosine kinase receptor resulted in a significant reduction in telomerase activity, accompanied by a therapeutically relevant growth inhibition of cancer cells. Accordingly, the specification is enabling for methods which monitor and evaluate the efficacy of EGF and EGFR inhibitors. The prior art of Zhu teaches that TGF-β1 inhibits telomerase activity in tumor cells and the prior art of Sigala teaches that NGF suppresses telomerase activity in prostate cancer cells. However, the specification and prior art do not teach that all "growth factor cancer drugs" act via a mechanism which includes inhibition of telomerase activity. The specification provides no information regarding the effect of inhibitors of EGF, IGF, PDGF, neurotrophic factors, components of the MAP kinase pathway, MEK or src on telomerase activity. The findings obtained with EGF, TGF-β1 and NGF cannot be extrapolated to all growth factors or to all compounds which alter any signaling mechanism associated with a growth factor. Insufficient evidence has been provided to support the conclusion that altering the signaling pathway of any growth factor results in an inhibition in telomerase activity and an associated inhibition in cancer cell growth. Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of

ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, it is highly unpredictable as to whether a "growth factor cancer drug" will act by inhibiting telomerase activity and will cause an associated improvement in the cancer phenotype. In view of the high level of unpredictability in the art and lack of guidance provided in the specification, undue experimentation would be required to practice the invention as it is broadly claimed.

Response to arguments:

In the response of Paper No. 8, Applicants argue that there is no requirement that they show that all growth factor cancer drugs have the effect of reducing telomerase activity because the essential point of the method is to determine and monitor "the effect of a growth factor drug on telomerase activity and to correlate a reduction of telomerase activity with the therapeutic benefit of the drug." Applicants arguments have been fully considered but are not convincing because in order to practice the claimed method requires that one have an understanding of the how to interpret the results of the method. The claimed method is not one for screening for growth factors which inhibit telomerase activity, but rather one for evaluating the efficacy of a growth factor cancer drug by assaying for the drug's ability to inhibit telomerase activity. However, many growth factor cancer drugs do not act via a mechanism which inhibits telomerase

activity. The specification does not provide a predictable means for distinguishing between growth factors which act via a method of inhibiting telomerase activity versus growth factors that do not alter telomerase activity. Accordingly, the specification does not adequately teach one of skill in the art how to interpret the results of claimed method. As stated at page 6 of the response, "if a growth factor cancer drug does not, at a given dosage, have an effect on telomerase activity, it may be concluded that either the chosen dosage is not suitable to achieve a therapeutic effect, or, alternatively, the method is not appropriate for this particular scenerio, i.e., with regard to the individual to be treated or to the particular tumor type". Yet, the claims require "correlating the level of telomerase activity with the therapeutic effect of the growth factor cancer drug." However, a negative effect (i.e., no change in the level of telomerase activity) would not necessarily be indicative of the growth factor drug's efficacy since the growth factor may still be effective even if it does not act via a mechanism of inhibiting telomerase activity. The specification (page 5) clearly teaches that loss of telomerase activity in cells treated with some growth factor cancer drugs is not a result of merely decreasing the number of tumor cells. Thus, the claimed method is not based solely on the well known concept that a reduction in telomerase activity is correlated with an effective response to therapy. Rather, as stated at page 5 of the specification, "As opposed to classical chemotherapeutics or radiation, an objective response (defined as regression of tumor volume or eradication of cancer cells) during or after cancer therapy with growth factor drugs cannot be seen in patients within a short period of time because these drugs have no immediate cell killing activity. For these drugs, it is expected that an

objective response may be observed only after long term treatment... Furthermore, while telomerase activity has been suggested as a marker for monitoring chemotherapeutical and/or radiation treatments, in which the level of telomerase appears to be proportional to the number of remaining tumor cells, no markers have been available for monitoring the therapeutic effect of growth factor cancer drugs." Applicants have not provided sufficient guidance as to how to interpret the results of methods in which growth factor cancer drugs are utilized which do not act by inhibiting telomerase activity and thereby have not enabled one of skill in the art to practice methods of monitoring and evaluating the efficacy of any growth factor cancer drug in therapy by assaying for telomerase activity.

3. Claims 1-13 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-13 and 17 are indefinite over the recitation of "growth factor cancer drug". The specification discusses growth factor cancer drugs but does not provide a complete and fixed definition for this phrase. At page 6 of the specification, it is stated that the present invention "can be applied to monitoring the efficacy of the following growth factor cancer drugs: all growth factor cancer drugs which interfere with tyrosine kinase activities and/or with components of the deregulated intracellular signal transduction pathways downstream of the tyrosine kinase activities". It is unclear as to whether the claims are intended to include any

compound which effects the growth of a cancer cell or only compounds which effect art recognized growth factors.

Response to arguments:

In the response of Paper No. 8, Applicants cite pages 2-3 of the specification as providing a definition for the phrase "growth factor cancer drug". However, the specification states that the phrase "growth factor cancer drugs is used as a synonym for compounds that act by a mechanism defined above". The specification does not define a specific mechanism, but generically and broadly recites examples of mechanisms, such as, inhibition of tyrosine activity via a growth factor receptor, antibodies directed to the extracellular domain of any growth factor receptor or any compounds that interferes with a component of any deregulated intracellular signal transduction pathway. These are not specific mechanisms such that one of skill in the art could ascertain what would constitute a compound that acts via these "mechanisms".

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6, 8, 10, 11 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harley (US Patent No. 5,863,726) in view of Zhu et al (Proceedings of the National Academies of Sciences, USA (June 1996) 6091-6095).

Harley (see, for example, columns 2-3 and 25) teaches methods for monitoring the effectiveness of a cancer therapeutic wherein the methods comprise obtaining a sample of cells from a patient being treated with a cancer therapeutic, determining the level of telomerase activity in the sample, comparing the amount of telomerase activity present in the sample with a control, and evaluating the efficacy of the therapeutic based on a change in the level of telomerase activity in the sample. The level of telomerase activity may be determined by performing a TRAP assay in which a telomerase substrate is extended by the telomerase present in the sample and the extended telomerase substrate is amplified by PCR. Harley also teaches kits useful for performing methods which involve assaying telomerase activity (column 25). Harley states that the method can be used to monitor the effectiveness of any telomerase inhibitor. However, Harley does not teach specifically monitoring the effectiveness of the telomerase inhibitor TGF-β1.

Zhu teaches that telomerase activity is associated with the occurrence of cancer. The reference teaches that TGF-β1 inhibits telomerase activity and that this decrease in telomerase activity is accompanied by an inhibition of cancer cell growth (page 6093). TGF-β1 is considered to be a "growth factor cancer drug". The reference also teaches that cytotoxic agents which block the cell cycle, including methotrexate, 5-fluorouracil and doxorubicin also inhibit telomerase. These cytotoxic agents are considered to be "growth factor cancer drugs" and "an inhibitor of the signaling pathway triggered by the activation of a receptor" from a growth factor family since these compounds generically block the cell cycle and thereby indirectly block components of signaling pathways.

In view of the teachings of Zhu that TGF-β1, methotrexate, 5-fluorouracil and doxorubicin inhibit telomerase activity and inhibit proliferation of cancer cells, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Harley so as to have utilized TGF-β1, methotrexate, 5-fluorouracil or doxorubicin as the telomerase inhibitors in order to have provided an effective means for monitoring the effectiveness of these compounds in treating cancer.

Response to arguments:

In the response of Paper No. 8, Applicants traverse the above rejection on the grounds that "the Examiner has not established a suggestion or motivation to make the claimed combination in the prior art, nor has the Examiner demonstrated a reasonable expectation of success".

Applicants arguments have been fully considered but are not persuasive. Harley provides clear motivation for applying the screening methods to any "growth factor cancer drug". Harley (column 25) states that "The level of telomerase activity can also be used to monitor the effectiveness of chemotherapeutics during cancer treatment. The level of telomerase can be a monitor of the effectiveness of a telomerase inhibitor or retinoid therapy or any other cancer therapy, where telomerase activity is decreased through telomerase inhibition, cellular differentiation , or cell death, respectively. The level of telomerase can monitor the effectiveness of any oncolytic or tumor-debulking procedure providing an estimate of the number of immortal cells within the patient". Accordingly, Harley clearly suggests applying the disclosed method to monitoring the analysis of any cancer agent or telomerase inhibitor. Further, Applicants have provided no arguments as to why one of ordinary skill in the art would not have a reasonable expectation of success. As stated above, the method of Harley is applicable to any potential cancer drug or telomerase inhibitor and Zhu teaches that TGF-β1, methotrexate, 5-fluorouracil and doxorubicin inhibit telomerase activity and inhibit proliferation of cancer cells. Accordingly, the ordinary artisan would have more than a reasonable expectation of success of generating an effective method for monitoring and evaluating the efficacy of TGF-β1, methotrexate, 5-fluorouracil and doxorubicin by assaying for telomerase activity.

5. Claims 1-3 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harley (US Patent No. 5,863,726) in view of Sigala (Clinical Cancer Research (May 1999) 5: 1211-1218).

Harley (see, for example, columns 2-3 and 25) teaches methods for monitoring the effectiveness of a cancer therapeutic wherein the methods comprise obtaining a sample of cells from a patient being treated with a cancer therapeutic, determining the level of telomerase activity in the sample, comparing the amount of telomerase activity present in the sample with a control, and evaluating the efficacy of the therapeutic based on a change in the level of telomerase activity in the sample. The level of telomerase activity may be determined by performing a TRAP assay in which a telomerase substrate is extended by the telomerase present in the sample and the extended telomerase substrate is amplified by PCR. Harley also teaches kits useful for performing methods which involve assaying telomerase activity (column 25). Harley states that the method can be used to monitor the effectiveness of any telomerase inhibitor. However, Harley does not teach specifically monitoring the effectiveness of the telomerase inhibitor NGF.

Sigala teaches that telomerase activity is associated with the occurrence of prostate cancer. The reference also teaches that nerve growth factor suppresses telomerase activity and that this decrease in telomerase activity is accompanied by an inhibition of prostate cancer cell growth (page 1216). Sigala further teaches that two metastatic prostate cancer cell lines treated with NGF reverted to slowly proliferating, noninvasive phenotypes characterized by very low telomerase activity. It is noted that NGF is considered to be a "growth factor cancer drug".

In view of the teachings of Sigala that NGF inhibits telomerase activity and inhibits proliferation of prostate cancer cells, it would have been obvious to one of ordinary skill in the

art at the time the invention was made to have modified the assay of Harley so as to have utilized NGF as the telomerase inhibitor in order to have provided an effective means for monitoring the effectiveness of NGF in treating prostate cancer.

Response to arguments:

In the response of Paper No. 8, Applicants traverse the above rejection on the grounds that "the Examiner has not established a suggestion or motivation to make the claimed combination in the prior art, nor has the Examiner demonstrated a reasonable expectation of success".

Applicants arguments have been fully considered but are not persuasive. Harley provides clear motivation for applying the screening methods to any "growth factor cancer drug". Harley (column 25) states that "The level of telomerase activity can also be used to monitor the effectiveness of chemotherapeutics during cancer treatment. The level of telomerase can be a monitor of the effectiveness of a telomerase inhibitor or retinoid therapy or any other cancer therapy, where telomerase activity is decreased through telomerase inhibition, cellular differentiation , or cell death, respectively. The level of telomerase can monitor the effectiveness of any oncolytic or tumor-debulking procedure providing an estimate of the number of immortal cells within the patient". Accordingly, Harley clearly suggests applying the disclosed method to monitoring the analysis of any cancer agent or telomerase inhibitor. Further, Applicants have provided no arguments as to why one of ordinary skill in the art would not have a reasonable expecation of success. As stated above, the method of Harley is applicable to any potential

cancer drug or telomerase inhibitor and Sigala teaches that NGF suppresses telomerase activity and that this decrease in telomerase activity is accompanied by an inhibition of prostate cancer cell growth. Accordingly, the ordinary artisan would have more than a reasonable expectation of success of generating an effective method for monitoring and evaluating the efficacy of NGF by assaying for telomerase activity.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703)-308-1152. The fax number for the Technology Center is (703)-305-3014 or (703)-305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

July 11, 2002

CARLA J. MYERS
PRIMARY EXAMINER